RESPONSE

I. Status of the Claims

Prior to the third Action, claims 1-19, 23, 51, 52, 94, 96-99, 102, 105-107, 111, 112, 115-117 and 120-122 were pending and have been examined. Presently, claims 1, 14, 18, 23, 94, 96-99 and 107 have been amended, without prejudice or disclaimer. Claims 2-13, 15-17, 19, 102, 105, 111, 115, 116, 120 and 121 have been cancelled, without prejudice or disclaimer. Claims 123-149 have been added, which are fully supported by the original application and drawn to inventions not patentably distinct from the examined claims. Should any small entity fees be deemed necessary for the new claims, such fees should be deducted from Peregrine Pharmaceuticals, Inc. Deposit Account No. 50-3493/4001.003000.

Claims 1, 14, 18, 23, 51, 52, 94, 96-99, 106, 107, 112, 117 and 122-149 are therefore in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Amendments to the Specification

The earlier amendments to the specification regarding characterization of the disclosed antibodies and regarding the 3B10 antibody have all been entered. The earlier amendments to certain paragraphs of the specification to clarify the relationship between the variable region sequences of the 3G4 antibody, deposited before the priority date, and the CDR sequences contained within the variable regions have also all been entered. Applicants appreciate the Examiner's agreement on these issues.

The present application, filed July 15, 2003, is one of the priority applications for a number of related and co-pending applications each filed August 15, 2003, which all claim priority to the same provisional application, filed July 15, 2002. The related applications include

application Serial No. 10/642,118 ("the '118 application"), which issued as U.S. Patent No. 7,247,303 on July 24, 2007 ("the '303 patent"; Attorney Docket No. 4001.003085); application Serial No. 10/642,058 ("the '058 application"; Attorney Docket No. 4001.003084); and application Serial No. 10/642,116 ("the '116 application"; Attorney Docket No. 4001.003087).

In the '303 patent (**Exhibit A**), the '058 application, the '116 application and other co-pending applications, the sequence clarifications have also been accompanied by entry of new SEQ ID NOs: for the CDRs and submission of a new sequence listing. In the present case, although the heavy and light chain CDR sequences are already defined by their positions within SEQ ID NO:2 and SEQ ID NO:4, Applicants now elect to assign new SEQ ID NOs: to the CDRs, in the same manner as in the '303 patent and, *e.g.*, the '058 and '116 applications.

Accordingly, the VH CDR1, CDR2 and CDR3 are now assigned as SEQ ID NO:10, NO:11 and NO:12; the VL CDR1, CDR2 and CDR3 are now assigned as SEQ ID NO:13, NO:14 and NO:15; and the specification has been amended accordingly. A new sequence listing disc, paper copies and the required sequence statement are also enclosed herewith. All such actions match those taken in the '303 patent.

In addition to the '303 patent, particular support for the sequence amendments was set forth in Applicants' supplemental response to the first Official Action in the present application, when certain changes to the specification were made. The present amendments are thus supported throughout the specification as filed, for example, in the general description of CDRs at pages 67-70 and the references incorporated therein by reference, particularly from page 67, line 15 to page 68, line 24 and Kabat *et al.*, "Sequences of Proteins of Immunological Interest" 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, pp 647-669, 1991; in

the particular description of the CDR sequences of the 3G4 antibody in Example XIX (pages 279-282), FIG. 18A, FIG. 18B, SEQ ID NO:2 and SEQ ID NO:4; and in the relationship between the general CDR description and the specific data and teaching regarding the deposited 3G4 antibody (which sections match the '118 application at pages 82-85, particularly page 82, line 15 to page 83, line 25, Kabat *et al.*, 1991; and Example XIX at pages 308-310).

In summary, the present amendments to the specification are therefore proper and should be entered.

III. The Present Claims are Not Patentably Distinct

Prior to the third Action, the claims in the present application were drawn to particular unconjugated or "naked" antibodies; hybridomas producing the antibodies; methods for preparing the antibodies; and compositions and pharmaceuticals of the antibodies. Independent claims 117, 122, 106 and 112, which are allowed, recite the antibodies, hybridomas, compositions and pharmaceuticals, respectively, in terms of the deposited 3G4 antibody. Independent claims 97, 98, 1 (and 94 & 107) and 96 defined the antibodies, hybridomas, compositions and pharmaceuticals, respectively, in other structural and functional terms.

Presently, hybridoma claims are being submitted that define the produced antibody as comprising two variable regions with defined CDR sequences (claims 98 and 130) or entire variable region sequences (claim 131).

Counterparts to such claims, but drawn to the antibodies, compositions and pharmaceuticals, are already represented by dependent claims issued in the above-referenced, '303 patent (**Exhibit A**). Accordingly, the present compositions (claims 1, 94 and 107) and pharmaceuticals (claim 96) have each been revised to further recite the addition of at least a second therapeutic agent, and the antibody (claim 97) is now a kit claim, which also recites at

least a second therapeutic agent. The present compositions (claims 1, 94 and 107), pharmaceuticals (claims 96 and 148) and kits (claims 97 and 149) recite the claimed antibody as comprising two variable regions with defined CDR sequences, but claims drawn to the entire variable region sequences are not included within these claim sets.

Composition, pharmaceutical and kit claims that include at least a second therapeutic agent and define the claimed antibody as comprising either or both of the entire variable region sequences are pending in the above-referenced, '116 application and have been indicated to be allowable (see, *e.g.*, corrected Office Action dated November 27, 2007 and Interview Summary in the '116 application).

In the second Official Action in the present application, an obviousness-type double patenting rejection was entered over the '116 application. That rejection established that claims drawn to the antibodies, compositions and pharmaceuticals alone, and claims drawn to the compositions, pharmaceuticals and kits in combination with at least a second therapeutic or anti-cancer agent, all constitute a single invention, each set of claims not patentably distinct from the other[1]. In response to the obviousness-type double patenting rejection, Applicants submitted a terminal disclaimer over the '116 application.

Therefore, the claims drawn to compositions, pharmaceuticals and kits comprising the claimed antibodies in combination with at least a second therapeutic or anti-cancer agent, as now submitted, are to be properly entered in the present application. As the Office has affirmatively determined that all such single agent compositions and combinations with at least two agents are drawn to a single, patentably indistinct invention, disclosed in the present specification, the foregoing amendment is proper for entry into the present application.

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[1]No restriction requirements have been entered between these sets of claims in the present application or in the '116 application.

For the record, the first Official Action in the present application also entered an obviousness-type double patenting rejection over the '118 application (now the '303 patent). In response, Applicants submitted a terminal disclaimer over the '118 application.

IV. Support for the Claims

Support for the revised and new claims exists throughout the specification and claims of the original and parent applications and in the pending claims.

Claim 1 has first been revised to recite the addition of at least a second therapeutic agent, which reflects an invention that is not patentably distinct from the invention of the claims already examined in the present application. The 'at least a second therapeutic agent' language is supported throughout the present specification, for example, first in the specification from page 30, line 26 to page 31, line 7, particularly at page 30, line 34 and at page 31, lines 6 and 7.

Claim 1 has also been revised to define the recited antibody in terms of the variable regions of the 3G4 antibody, deposited before the priority date and recited in the original claims. In particular, to recite that the antibody or antigen-binding fragment thereof comprises at least two variable regions, which each comprise three CDRs, wherein the variable regions are the heavy or light chain variable regions of the deposited 3G4 antibody, the CDR sequences of which are recited in the claim. The language inserted is based upon that issued from the above-referenced, '118 application, which issued as the '303 patent (**Exhibit A**). However, present claim 1 specifies that the antibody comprises at least two variable regions, whereas the claims issued in the '303 patent include antibodies with only a single variable region.

The revisions to claim 1 are also supported throughout the present application. For example, in the specification at least at page 41, lines 16-24; at pages 67-70; Example XIX (pages 279-282); in FIG. 18A and FIG. 18B; SEQ ID NO:2 and SEQ ID NO:4; and in the

originally deposited antibody itself. In the description of CDRs in the specification at pages 67-70, support for claim 1 also exists in the references incorporated therein by reference, particularly Kabat *et al.*, "Sequences of Proteins of Immunological Interest" 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, pp 647-669, 1991.

Claims 14, 18 and 23 have each been revised so that their language better accords with that of claim 1.

Claim 94 has been revised as in claim 1, and is thus supported as set forth above for claim 1.

Independent claim 96, the pharmaceutical counterpart to claim 1, has been revised to recite the addition of at least a second therapeutic agent and to define the antibody, or antigen-binding fragment thereof, in terms of the CDR sequences of the variable regions of the deposited 3G4 antibody. These revisions are supported as set forth above for claim 1.

Independent claim 97 has been revised to be a kit claim counterpart to claim 1. The addition of at least a second therapeutic agent and the definition of the claimed antibody, or antigen-binding fragment thereof, are supported as set forth above for claim 1. The 'in at least a first container' language is supported throughout the present specification, for example, first in the specification from page 30, line 26 to page 31, line 7, particularly at page 30, line 35.

Independent claim 98, drawn to a hybridoma, has been revised to define the recited antibody in terms of the CDR sequences of the variable regions of the deposited 3G4 antibody. These revisions are supported as set forth above for claim 1.

Method claim 99 has also been revised to define the antibody produced in terms of the CDR sequences of the variable regions of the deposited 3G4 antibody. These revisions are supported as set forth above for claim 1.

Independent claim 107 has been revised to specify that the antibody or antigen-binding fragment thereof comprises both the heavy and light chain variable regions of the deposited 3G4 antibody, as defined in terms of the recited CDR sequences. This language matches claim 4 issued in the '303 patent, and is supported throughout the specification of the present application, for example, in the specification at least at page 41, lines 16-24; at pages 67-70; Example XIX (pages 279-282); in FIG. 18A and FIG. 18B; and in the originally deposited antibody itself.

New claim 123 is an independent claim based upon allowed claim 106, but reciting the deposited antibody "or an antigen-binding fragment thereof". This is supported throughout the specification and claims of the present application, for example, by original claim 14.

New claim 124 further limits claim 123 by separately reciting the antigen-binding fragment.

New claim 125 further limits claim 124 by reciting that the antigen-binding fragment is operatively attached to a human antibody constant region. This matches claim 13 issued in the '303 patent and is supported throughout the specification and claims of the present application, for example, in Example XIX (pages 279-282) and in original claims 17-19, particularly claim 18.

New claim 126 is an independent claim based upon allowed claim 112, but reciting the deposited antibody "or an antigen-binding fragment thereof". New claims 127 and 128 further limit claim 126 by separately reciting the antigen-binding fragment and operative attachment to a human antibody constant region. These three claims are counterparts to claims 123, 124 and 125, and are supported as set forth above for those claims.

New claim 129 is an independent claim based upon allowed claim 117, but reciting the deposited antibody "or an antigen-binding fragment thereof". This is a counterpart to independent claims 123 and 126, and is supported as set forth above for those claims.

New independent claim 130 is a hybridoma claim counterpart to current claim 107, and thus specifies that the antibody comprises both the heavy and light chain variable regions of the deposited 3G4 antibody, as defined in terms of the recited CDR sequences. This is supported as set forth above for claim 107.

New independent claim 131 is a hybridoma claim that defines the heavy and light chain variable regions of the deposited 3G4 antibody in terms of SEQ ID NO:2 and SEQ ID NO:4. This language matches that of claims 8 and 9 issued in the '303 patent, and is supported throughout the present specification as filed, such as at least at page 17, lines 10-16, particularly line 12; page 41, lines 16-24, particularly lines 18-19; page 68, lines 13-18, particularly line 14; in Example XIX, such as at page 280, lines 3-5 and 22-24; and in FIG. 18A and FIG. 18B.

New dependent claims 132, 133 and 134 separately recite embodiments of claim 1, *i.e.*, the heavy, light and heavy/light chains. These claims match the language of claims 2, 3 and 4 issued in the '303 patent, respectively. These claims are supported throughout the specification and claims of the present application, for example, in the specification at least at page 41, lines 16-24; pages 67-70; pages 279-282; in FIG. 18A and FIG. 18B; and in the originally deposited antibody itself.

New claim 135 further limits claim 1 by reciting that the second therapeutic agent is a second anti-cancer agent. This is supported throughout the present specification, for example, first in the specification from page 30, line 26 to page 31, line 7, particularly at page 30, line 32 and at page 31, line 7.

New dependent claims 136-141 separately recite embodiments of claim 96 in terms of heavy, light and heavy/light chains (claims 136, 137 and 138), antigen-binding fragments (claim 139), operative attachment to a human antibody constant region (claim 140) and second anti-cancer agents (claim 141). These are counterparts to current claims 132-134, 14, 18 and 135, respectively, and are supported as set forth above for those claims.

New dependent claims 142-147 separately recite embodiments of claim 97 in terms of heavy, light and heavy/light chains (claims 142, 143 and 144), antigen-binding fragments (claim 145), operative attachment to a human antibody constant region (claim 146) and second anti-cancer agents (claim 147). These are counterparts to current claims 132-134, 14, 18 and 135, respectively, and are supported as set forth above for those claims.

New independent claim 148 is a pharmaceutical claim counterpart to current claim 107, and thus specifies that the antibody comprises both the heavy and light chain variable regions of the deposited 3G4 antibody, as defined in terms of the recited CDR sequences. This is supported as set forth above for claim 107.

Finally, new independent claim 149 is a kit claim counterpart to current claim 107, and thus specifies that the antibody comprises both the heavy and light chain variable regions of the deposited 3G4 antibody, as defined in terms of the recited CDR sequences. This is supported as set forth above for claims 97 and 107.

It will therefore be understood that no new matter is included within any of the amended claims.

V. Issued and Allowed Claims and Response Summary

In the third Action, the previous objection to the specification and rejections under 35 U.S.C. § 101, § 112, first paragraph (new matter and written description), § 102(b) and for obviousness-type double patenting have been withdrawn, in whole or part. Applicants appreciate the withdrawal of the objection and rejections.

Although most claims are newly rejected, Applicants appreciate the examiner's guidance on overcoming the present rejections, both as set forth in this Action and in related applications in which the same issues were raised and rejections overcome. In particular, claims 106, 112, 117 and 122 are already allowed in the present application. Claims with CDR language similar to that of the present claims have issued in the above-referenced '303 patent (**Exhibit A**). Moreover, claims with the same CDR language as now used in this application are essentially in condition for allowance in the above-referenced '058 application[2], which was also examined by Examiner Goddard.

In this light, Applicants first elect to progress this application to issue based on the claims already allowed. Accordingly, independent claims 106, 112, 117, 122, 123, 126 and 129, and all claims dependent thereon, are now allowed.

In addition, all remaining claims have been placed in condition for allowance using CDR and sequence language based upon that allowed by Examiner Goddard and issued in the '303 patent (**Exhibit A**), and corresponding to the essentially allowable claims in the '058 application. Therefore, independent claims 1, 94, 96, 97, 98, 99, 107, 130, 148 and 149, and all claims dependent thereon, are also allowable.

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[2]In the third Official Action (dated March 11, 2008) in the '058 application, combination treatment method claims using the same language as now recited in the pending claims were free from all rejections except for obviousness-type double patenting.

Independent claim 131, drawn to a hybridoma, is further allowable, based on the entire variable region sequences. This reasoning is also supported by issued claims in the '303 patent and allowable claims in co-pending applications, including the '058 application.

In the present response, Applicants have also taken care to address any issues of double patenting between this application, the '303 patent and the '116 application (see also, **Section III**). Firstly, terminal disclaimers with respect to the '303 patent and the '116 application are already of record in the present application. Secondly, in the present application, the single-agent composition claims reciting CDR and variable region sequence language are limited to the hybridoma claims. Thirdly, claims in the present application that also recite at least a second therapeutic or anti-cancer agent are drafted in terms of the defined CDR sequences, and do not include language to the deposited antibody or to the entire variable region sequences.

All claims are therefore in condition for allowance, based upon the allowed claims in the present application, the present response and other evidence, including issuance of the '303 patent and examination of the '058 application.

VI. Enablement Rejection Under 35 U.S.C. § 112, First Paragraph

The third Action at pages 2-11 newly rejects claims 1-19, 23, 51, 52, 94, 96-99, 102, 105, 107, 111, 115, 116, 120 and 121 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support in the specification. Although Applicants respectfully traverse, the rejection is overcome. In particular, and without acquiescing with the present rejection in any way, Applicants elect to place the application in condition for issue using two approaches.

Firstly, using claims reciting the deposited 3G4 antibody, or an antigen-binding fragment thereof, including the claims already allowed. Accordingly, independent claims 106, 112, 117, 122, 123, 126 and 129, and all claims dependent thereon, are allowed on this basis.

Secondly, the rejection is overcome using claims reciting the defined CDR and variable region sequences of the deposited 3G4 antibody, which language has already been accepted by the Office in the related applications. In particular, claims with CDR language similar to that of the present claims have issued in the counterpart '303 patent (**Exhibit A**) and, importantly, claims with the same CDR language as in the present claims are essentially in condition for allowance in the co-pending, '058 application.

In addition to the issued claims in the '303 patent and allowable claims in the co-pending applications, including the '058 application, claims of the present language are enabled according to the teaching in the specification and the knowledge in the art regarding antibody CDR and variable region sequences.

For example, it has been scientifically established that six CDRs are not required for antibody binding, which is believed to be acknowledged by current Office policy. Indeed, there is significant scientific evidence to support such a conclusion. For instance, single domain antibodies, *i.e.*, those with three CDRs, are common, and can correspond to the variable regions of either the heavy (V_H) or light (V_L) chains of human antibodies. Other single domain antibodies are camelid and camelized antibodies, which are devoid of light chains.

Not only are three CDRs entirely sufficient, published evidence shows that two and even one CDR is sufficient for antigen binding. Two CDRs are able to retain the antigen recognition capacity of their parent molecules. For example, see Qiu *et al.*, *Nature Biotechnology*, 25(8):921-929, 2007 (**Exhibit B**), in which small constructs containing only two CDRs were not only able to retain the antigen recognition capacity of their parent molecules, but also had a superior capacity to penetrate tumors (Qiu throughout, *e.g.*, abstract).

In addition, various single CDRs have been shown to confer specific antibody binding activities. For example, see Kiss *et al.*, *Nucleic Acids Research*, 34(19):e132, 2006 (**Exhibit C**), in which a single CDR from a lysozyme-binding antibody is shown to confer lysozyme-binding activity (Kiss throughout, *e.g.*, abstract).

Moreover, the introduction section of Kiss describes various other successful uses of single CDRs to confer effective antibody binding (Kiss at page 2, column 1, citing references 43, 44, 45 and 46, listed in Kiss at page 14). Kiss extends the earlier work by showing the general applicability of using a single CDR to confer effective antibody binding functions (Kiss throughout, *e.g.*, introduction and discussion). Kiss also quotes Casset *et al.*, *BBRC*, 307:198-205, 2003, as teaching that CDR1 from a CD4 binding antibody confers CD4 binding activity (Kiss at page 2, column 1, citing reference 45, which is Casset *et al.*, 2003).

Thus, antibodies with three, two and a single CDR are enabled. Indeed, the claims issued in the '303 patent include constructs in which only a single variable region, *i.e.*, three CDRs, is defined. Nonetheless, and without acquiescing with the present rejection in any way, all pending claims recite antibodies containing at least two variable regions that each comprises three CDRs, *i.e.*, have six CDRs in total.

Independent claims 1, 94, 96, 97, 98, 99, 107, 130, 148 and 149, and all claims dependent thereon, are first allowed on the basis of reciting at least two variable regions with the defined CDR sequences. In addition to the issued claims in the '303 patent, note that claims of the same language as now pending have essentially been allowed in the co-pending, '058 application.

Independent claim 131 is also allowed on the basis of reciting two variable regions along with the entire variable region sequences. In addition to the '303 patent, other claims of this

language have again been indicated to be allowable in the related applications, including the above-referenced, '058 application and '116 application".

There is considerable scientific evidence of the enabling support for such claim language. For example, such claims cover antibodies generated by the technique of chain shuffling, well-established in the art prior to the present invention and further disclosed in this application, including numerous U.S. patents incorporated into the application by reference. Chain shuffling has been practiced for well over a decade and, by way of example only, one of the early seminal publications on chain shuffling is Marks *et al.*, *BioTechnology*, 10:779-783, 1992 **(Exhibit D)**.

In summary, the enablement rejection under 35 U.S.C. § 112, first paragraph is therefore overcome and should be withdrawn.

VII. First Anticipation Rejection Under 35 U.S.C. § 102(b)

The third Action at pages 11-14 modifies the earlier anticipation rejection under 35 U.S.C. § 102(b) over Maneta-Peyret *et al.*, *J. Immunol. Methods*, 108:123-127, 1988 ("Maneta-Peyret"), which is now applied to claims 1-11, 23, 94, 96, 97, 102 and 115 as allegedly being anticipated by Maneta-Peyret as evidenced by Bevers *et al.*, *Clin. Immunol.*, 112:159-160, 2004 ("Bevers"). Although Applicants respectfully traverse, the rejection is overcome.

Applicants maintain the position from their second response, which reasoning is incorporated herein by reference. Applicants also note that Bevers, published in 2004, is a post-filing date reference.

Nonetheless, and without acquiescing with the present rejection in any way, Applicants elect to place the application in condition for issue using two groups of claims that are already acceptable to the Office.

Firstly, using claims reciting the deposited 3G4 antibody, or an antigen-binding fragment thereof, including the claims already allowed. Accordingly, independent claims 106, 112, 117, 122, 123, 126 and 129, and all claims dependent thereon, are allowed on this basis.

Secondly, appreciating that claims reciting defined CDR and variable region sequences have issued or are allowable in the related applications, the remaining claims have been placed in condition for allowance by reciting the defined CDR and variable region sequences of the deposited 3G4 antibody. Accordingly, independent claims 1, 94, 96, 97, 98, 99, 107, 130, 131, 148 and 149, and all claims dependent thereon, are also allowable. This is in accordance with issuance of the '303 patent **(Exhibit A)** and with claims essentially in condition for allowance in the '058 application.

The first anticipation rejection, under 35 U.S.C. § 102(b), is thus overcome and should be withdrawn.

VIII. Second Anticipation Rejection Under 35 U.S.C. § 102(b)

The third Action at pages 14-20 modifies the earlier anticipation rejection under 35 U.S.C. § 102(b) over PCT publication WO 00/02584 by Thorpe and Ran, which is now applied to claims 1-19, 23, 51, 52, 94, 96-98, 102, 107, 115 and 120 as allegedly being anticipated by WO 00/02584 as evidenced by Bevers. Although Applicants respectfully traverse, the rejection is overcome.

Applicants maintain the position from their second response, which reasoning is incorporated herein by reference. It is emphasized that it is the burden of the Office, in the first instance, to establish a proper anticipation rejection and not that of the Applicants to defend their disclosure. Thus, the appropriate standard is for the Office to establish that each and every element of the claimed invention does exist in the cited prior art reference, not for Applicants to

demonstrate "that it would not be expected that any monoclonal or polyclonal antibodies taught by the prior art could have the claimed binding profiles or binding affinity as referenced to 3G4 in claim 1" (third Action at page 19; emphasis added). Applicants also note that Bevers, published in 2004, is a post-filing date reference.

However, and without acquiescing with this rejection in any way, Applicants elect to place the application in condition for issue using two groups of claims that are already acceptable to the Office.

Firstly, using claims reciting the deposited 3G4 antibody, or an antigen-binding fragment thereof, including the claims already allowed. Accordingly, independent claims 106, 112, 117, 122, 123, 126 and 129, and all claims dependent thereon, are allowed on this basis.

Secondly, appreciating that claims reciting defined CDR and variable region sequences have issued or are allowable in the related applications, the remaining claims have been placed in condition for allowance by reciting the defined CDR and variable region sequences of the deposited 3G4 antibody. Accordingly, independent claims 1, 94, 96, 97, 98, 99, 107, 130, 131, 148 and 149, and all claims dependent thereon, are also allowable. This is in accordance with issuance of the '303 patent (**Exhibit A**) and with claims essentially in condition for allowance in the '058 application.

The second anticipation rejection, under 35 U.S.C. § 102(b), is therefore overcome and should be withdrawn.

IX. Third Anticipation Rejection Under 35 U.S.C. § 102(b)

The third Action at pages 20-24 newly rejects claims 1-12, 23, 51, 52, 94, 96-98, 102, 115 and 120 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,300,308 to Alan J. Schroit ("Schroit"), as evidenced by Bevers. Although Applicants respectfully traverse, the rejection is overcome.

Schroit is cited only under 35 U.S.C. § 102(e), and the issue date of Schroit precludes its citation under 35 U.S.C. § 102(b). Applicants therefore have the option to remove Schroit as prior art under 37 C.F.R. § 1.131, *i.e.*, by swearing behind Schroit. Applicants elect, however, to address the limitations of Schroit and to respond to the present rejection on the merits. This choice should not be interpreted as waiving the option to establish a date of invention earlier than any effective filing date of Schroit.

A rejection on the grounds of anticipation requires the disclosure, in a single reference, of every element of a claimed invention and requires that each and every facet of the claimed invention be identified in the applied reference. *Ex parte Levy*, 17 USPQ2d 1461 (B.P.A.I. 1990); *Minnesota Mining & Mfg. v. Johnson & Johnson Orthopaedics, Inc.*, 24 USPQ2d 1321 (Fed. Cir. 1992).

Applicants again point out that Bevers, published in 2004, is a post-filing date reference.

Applicants also respectfully point out that the third Action has misinterpreted Schroit's data as to the binding affinity of the antibodies, as shown in Figure 3. In contrast to the third Action at page 22, the Schroit data do not demonstrate that the polyclonal antibodies bind to PS, PE, PA and PG. Rather, Schroit in Figure 3 and at column 23, lines 54-67 first teaches that Schroit's polyclonal antiserum "reacted with PS and DOPE, but not with PC or other negatively charged phospholipids" (Schroit at column 23, lines 58-59), *i.e.*, not with PC, PA or PG. This is

shown in Schroit at FIG. 3B. Schroit at column 23, lines 60-67 next explains that the reaction to DOPE is not polar head group-specific, which is shown in FIG. 3C.

Thus, and as taught by Schroit throughout, Schroit's antibodies are specific for PS, which indeed, was the objective sought by Schroit and overcame the deficiencies of the art prior to Schroit (see, *e.g.*, Schroit at column 2, lines 16-40). Accordingly, the third Action at pages 22-23 is in incorrect in the position that it "would be expected that a subset of the polyclonal or monoclonal antibodies or antibodies produced by hybridomas taught by Schroit would have substantially the same phospholipid binding profile as the monoclonal antibody 3G4".

The rejection is therefore improper and should be withdrawn on this ground.

In addition, as to those pending claims drawn to compositions, pharmaceuticals and kits comprising the claimed antibodies and at least a second therapeutic or anti-cancer agent, Schroit does not include any such teaching. Presumably, this is in large part due to the fact that Schroit concerns administering PS-polypeptide conjugates, which are given as immunogens to generate anti-PS antibodies *in situ*. Whatever the reason, Schroit does not teach a composition, pharmaceutical or kit comprising any anti-PS antibody, irrespective of its structural or functional characteristics, and a second therapeutic or anti-cancer agent[3].

The rejection is thus improper, and should be withdrawn, on this additional ground.

Nonetheless, and without acquiescing with the present rejection in any way, this application has been placed in condition for issue using two groups of claims that are already acceptable to the Office.

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[3]Even when concerning kits with second or third containers, Schroit still does not teach any anti-PS antibody in combination with a second therapeutic or anti-cancer agent, but only in combination with "a matrix, solution, or other suitable delivery device", a "buffer, diluent or solvent" or a "detectable imaging agent" (*e.g.*, Schroit from column 7, line 39 to column 8, line 23).

Firstly, using claims reciting the deposited 3G4 antibody, or an antigen-binding fragment thereof, including the claims already allowed. Accordingly, independent claims 106, 112, 117, 122, 123, 126 and 129, and all claims dependent thereon, are allowed on this basis.

Secondly, appreciating that claims reciting defined CDR and variable region sequences have issued or are allowable in the related applications, the remaining claims have been placed in condition for allowance by reciting the defined CDR and variable region sequences of the deposited 3G4 antibody. Accordingly, independent claims 1, 94, 96, 97, 98, 99, 107, 130, 131, 148 and 149, and all claims dependent thereon, are also allowable. This accords with the '303 patent (**Exhibit A**) and the claims essentially in condition for allowance in the '058 application.

The third anticipation rejection, under 35 U.S.C. § 102(e), is therefore overcome and should be withdrawn.

X. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and accompanying documents, the present application is in condition for allowance and such favorable action is respectfully requested. Should Examiner Goddard have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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